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(54) **Quinoline derivatives and pharmaceutical composition containing them**

Quinolin-Derivate und diese enthaltende pharmazeutische Zusammensetzungen

Dérivés de quinoléine et compositions pharmaceutiques les contenant

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(73) Proprietor: **TAKEDA CHEMICAL INDUSTRIES, LTD.**
Chuo-ku, Osaka 541 (JP)

(72) Inventors:
- **Sohda, Takashi**
 Takatsuki, Osaka 569 (JP)
- **Makino, Haruhiko**
 Kawabe-gun, Hyogo 666-02 (JP)
- **Baba, Atsuo**
 Ashiya, Hyogo 659 (JP)

(74) Representative:
von Kreisler, Alek, Dipl.-Chem. et al
Patentanwälte,
von Kreisler-Selting-Werner,
Bahnhofsvorplatz 1 (Deichmannhaus)
50667 Köln (DE)

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EP-A- 0 567 107
EP-A- 0 608 870
EP-A- 0 634 169
FR-A- 2 134 169

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EP 0 686 630 B1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a novel quinoline derivative useful as an anti-inflammatory agent, particularly an agent for treating arthritis, or a salt thereof. The present invention also relates to a pharmaceutical composition containing the novel quinoline compound.

BACKGROUND OF THE INVENTION

[0002] Arthritis is an inflammatory disease of arthroses. Main examples of arthritis are rheumatoid arthritis and its analogous diseases wherein inflammation is observed in arthroses.

[0003] In particular, rheumatoid arthritis, also referred to as chronic rheumatism, is polyarthritis chronica whose main lesion is inflammatory changes in synovial membranes of, internal layers of articular capsules. Arthritis such as rheumatoid arthritis is progressive and causes articular disorders such as articular deformation, tetany, etc. When an effective treatment is not carried out and the disease worsens, serious physical disorders are often caused.

[0004] Hitherto, in treatment of such arthritis, chemotherapy has been carried out using steroids such as adrenal cortical hormones (e.g., cortisone, etc.), etc.; non-steroidal anti-inflammatory agents such as aspirin, piroxicam, indomethacin, etc.; gold preparations such as gold thiomalate, etc.; antirheumatic agents such as chloroquine preparations, D-penicillamine, etc.; antipodagrics such as colchicine, etc.; immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, levamisole, etc.

[0005] However, these drugs have problems such as serious side effects, side effects making their long-term use difficult, insufficient efficacy, inefficacy against arthritis which has already produced the symptoms.

[0006] Therefore, in clinical treatment of arthritis, drugs having low toxicity and excellent effects in the prophylaxis and treatment of arthritis have been required.

[0007] Various quinoline derivatives having an acyl group, hydroxyalkyl group or amidated carboxyl group at the 3-position have been synthesized. For example, Journal of Heterocyclic Chemistry, Vol. 12, p. 737 (1975) discloses 4-phenylquinoline derivatives having a hydroxymethyl group or amidated carboxyl group at the 3-position. The Journal of Organic Chemistry, Vol. 31, p. 3852 (1966) and Nippon Kagaku Zasshi, Vol. 90, p. 81 (1969) disclose 4-phenylquinoline derivatives having an acetyl group at the 3-position. Further, Chemical Abstracts, Vol. 79, 42371h (1973) discloses anti-inflammatory activity of 3-acylquinoline derivatives. The substitutents at the 2-position of the compounds disclosed in these literature are, however, limited to an alkyl group, phenyl group, etc.

[0008] Further to be mentioned are EP-A-0 567 107, EP-A-0 608 870 and EP-A-0 634 169.

OBJECTS OF THE INVENTION

[0009] The main object of the present invention is to provide a novel quinoline derivative having anti-inflammatory activity.

[0010] Another object of the present invention is to provide a pharmaceutical composition, particularly an anti-inflammatory composition, containing a quinoline derivative.

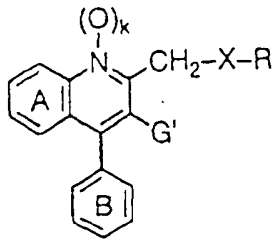
[0011] These objects as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description.

SUMMARY OF THE INVENTION

[0012] The present inventors have found that novel 4-phenylquinoline derivatives which contain at the 2-position an alkylene group having an optionally substituted amino group, and at the 3-position an acyl group have anti-inflammatory activity, and are useful as an agent for inhibiting arthral destruction. Thus, the present invention has been completed.

[0013] The present invention provides:

(1) a compound of the formula (I):



(I)

wherein

G is an acyl group of the formula: -CO-R^3 in which R^3 is a C_{1-5} alkyl group;

X is an oxygen atom, a thio group, a sulfinyl group, a sulfonyl group or a group of the formula: -$(CH_2)_q$- in which q is an integer of 0 to 5;

R is an optionally substituted amino group of the formula: -N(R^1) (R^2) in which R^1 and R^2 are, the same or different,

(1) a hydrogen atom or
(2) an optionally substituted hydrocarbon group, the hydrocarbon group in the optionally substituted hydrocarbon group being a group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{3-7} cycloalkyl,

wherein the substituent(s) to the hydrocarbon group are one to three substituents of

(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group,

each of rings A and B may have one to four substituents selected from

(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group,

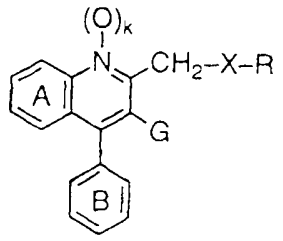
and further, rings A and B may have a substituent of -O-$(CH_2)_L$-O-, wherein L is an integer of 1 to 3, which forms a ring with mutually adjacent two carbons of the ring A or B;

k is 0 or 1, or a salt thereof,

(2) the compound of the above item (1), wherein G' is an acetyl group, or a salt thereof,
(3) the compound of the above item (1), wherein the ring A is substituted with at least one alkoxy group, or a salt thereof,
(4) the compound of the above item (3), wherein the ring A is substituted with the same or different two alkoxy groups, or a salt thereof,
(5) the compound of the above item (4), wherein the ring A is substituted with two alkoxy groups at the 6- and 7-positions of the quinoline ring, or a salt thereof,
(6) the compound of the above item (1), wherein the ring B is substituted with at least one alkoxy group, or a salt thereof,
(7) the compound of the above item (6), wherein the ring B is substituted with the same or different two alkoxy groups, or a salt thereof,
(8) the compound of the above item (7), wherein the ring B is substituted with two alkoxy groups at the 3- and 4-positions, or a salt thereof,
(9) the compound of the above item (1), wherein k is 0, or a salt thereof,
(10) the compound of the above item (1), which is 3-acetyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-

6,7-dimethoxyquinoline, or a salt thereof,

(11) a pharmaceutical composition comprising a compound of the formula (I):



(I)

wherein

G is an acyl group of the formula: -CO-R^3 in which R^3 is a C_{1-5} alkyl group;

x is an oxygen atom, a thio group, a sulfinyl group or a sulfonyl group or a group of the formula: -$(CH_2)_q$- in which q is an integer of 0 to 5;

R is an optionally substituted amino group of the formula: -N(R^1) (R^2) in which R^1 and R^2 are, the same or different,

(1) a hydrogen atom or

(2) an optionally substituted hydrocarbon group, the hydrocarbon group in the optionally substituted hydrocarbon group being a group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{3-7} cycloalkyl,

wherein the substituent(s) to the hydrocarbon group are one to three substituents of

(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group, and
(4) a thiol group or a C_{1-10} alkylthio group;

each of rings A and B may have one to four substituents selected from

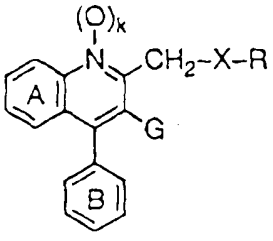
(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group, and
(4) a thiol group or a C_{1-10} alkylthio group, and further rings A and B may have a substituent of -O-$(CH_2)_L$-O-,

wherein L is an integer of 1 to 3, which forms a ring with mutually adjacent two carbons of the ring A or B;

k is 0 or 1,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier,

(12) an anti-inflammatory composition for pharmaceutical use, which comprises a compound of the formula (I):



(I)

wherein

G is an acyl group of the formula: -CO-R^3 in which R^3 is a C_{1-5} alkyl group;

X is an oxygen atom, a thio group, a sulfinyl group, a sulfonyl group or a group of the formula: -$(CH_2)_q$- in which q is an integer of 0 to 5;

R is an optionally substituted amino group of the formula: -N(R^1) (R^2) in which R^1 and R^2 are the same or different,

(1) a hydrogen atom or
(2) an optionally substituted hydrocarbon group, the hydrocarbon group in the optionally substituted hydrocarbon group being a group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{3-7} cycloalkyl,

wherein the substituent(s) to the hydrocarbon group are one to three substituents of

(1) a halogen atom,
(2) a C_{1-10} alykl group,
(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group;

each of rings A and B may have one to four substituents selected from

(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group,

and further rings A and B may have a substituent of -O-$(CH_2)_L$-O-, wherein L is an integer of 1 to 3, which forms a ring with mutually adjacent two carbons of the ring A or B;

k is 0 or 1,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier,
and
(13) use of a compound of the formula (I) or a salt thereof in the manufacture of anti-inflammatory compositions for pharmaceutical use.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The definitions of the symbols in the above formulas and their preferred examples are described below.

[0015] The optionally substituted amino group represented by R in the above formula (I) is represented by the formula: -N(R^1)(R^2) in which R^1 and R^2 are the same or different and are a hydrogen atom or an optionally substituted hydrocarbon group as defined above.

[0016] The hydrocarbon group of the optionally substituted hydrocarbon group represented by R^1 or R^2 includes aliphatic hydrocarbon groups and alicyclic hydrocarbon groups as defined above.

[0017] Examples of such aliphatic hydrocarbon groups include saturated aliphatic hydrocarbon groups (e.g., alkyl groups) having 1 to 8 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl and octyl; unsaturated aliphatic hydrocarbon groups (e.g., alkenyl groups) having 2 to 8 carbon atoms, such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl and 1-octenyl. In particular, ethyl and tert-butyl are preferred.

[0018] Examples of such alicyclic hydrocarbon groups include saturated alicyclic hydrocarbon groups (e.g., cycloalkyl groups) having 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0019] Each of the hydrocarbon groups represented by R^1 or R^2 may be unsubstituted or substituted with 1 to 3 substituents at any possible position.

[0020] The substituents of the hydrocarbon groups represented by R^1 or R^2 include aliphatic chain hydrocarbon groups, halogen atoms, an optionally substituted hydroxyl group, and an optionally substituted thiol group.

[0021] The aliphatic chain hydrocarbon group as the substituent of the hydrocarbon group represented by R^1 or R^2 include, for example, straight chain or branched alkyl groups, having 1 to 10 carbon atoms.

[0022] Preferred examples of the alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-

butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

[0023] Preferred examples of the cycloalkyl groups include those having 3 to 10 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]-octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo-[4.2.1]nonyl and bicyclo[4.3.1]decyl.

[0024] The halogen atom as the substituent of the hydrocarbon group represented by R^1 or R^2 includes, for example, fluorine, chlorine, bromine and iodine. In particular, fluorine and chlorine are preferred.

[0025] The optionally substituted hydroxyl group as the substituent of the hydrocarbon group or heterocyclic group represented by R^1 or R^2 includes, for example, a hydroxyl group and a hydroxyl group having an appropriate substituent such as a protective group for a hydroxyl group. Examples of the hydroxyl group having such a substituent include alkoxy, having 1 to 10 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy and cyclohexyloxy.

[0026] The optionally substituted thiol group as the substituent of the hydrocarbon group represented by R^1 or R^2 includes, for example, a thiol group and a thiol group having an appropriate substiuent such as a protecting group for a thiol group, i.e., alkylthio having 1 to 10 carbon atoms such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutyltho, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, and cyclohexylthio.

[0027] The substituent of the hydrocarbon group represented by R^1 or R^2 may have at least one, preferably 1 to 3, appropriate substituents.

[0028] Preferred examples of the optionally substituted amino group represented by R in the above formulas (I) include N,N-diethylamino and N-tert-butyl-N-ethylamino. The acyl group represented by G in the formula (I) is represented by the formula: $-CO-R^3$ in which R^3 is an alkyl group having 1 to 5 atoms such as methyl, ethyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl and 1-ethylpropyl. Preferred examples of the alkyl groups include methyl, butyl, isobutyl and pentyl.

[0029] Each of the ring A and ring B in the formula (I) may be substituted with at least one substituent. Examples of the substituent include halogen atoms,

alkyl groups, an optionally substituted hydroxyl group and an optionally substituted thiol group.

[0030] The halogen atom as the substituent of the ring A and ring B includes, for example, fluorine, chlorine, bromine and iodine. In particular, fluorine and chlorine are preferred.

[0031] The alkyl group as the substituent of the ring A and ring B is selected from straight-chain, branched or cyclic alkyl groups having 1 to 10 carbon atoms. Specific examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0032] The optionally substituted hydroxyl group as the substituent of the ring A and ring B includes a hydroxyl group, and a hydroxyl group having an appropriate substituent such as a protective group for a hydroxyl group, i.e., alkoxy groups having 1 to 10 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy.

[0033] The optionally substituted thiol as the substituent of the ring A and ring B includes a thiol group and a thiol group having an appropriate substituent such as a protective group for a thiol group, i.e., alkylthio groups having 1 to 10 carbon atoms such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, and cyclohexylthio.

[0034] The substituent of the ring A and ring B may be at any possible position in the rings. Preferably, the ring A is substituted at the 6 and/or 7 position(s) of the quinoline ring. Preferably, the ring B is substituted at the 3 and/or 4 position(s) of the ring B. Each of the rings may be substituted with the same or different 1 to 4 substituents. When the substituents of the ring A or ring B are adjacent to each other, the adjacent substituents are linked together to form a group of the formula: $-O-(CH_2)_L-O-$ wherein L is an integer of 1 to 3 which may form a 5- to 7-membered ring with carbon atoms of the benzene ring.

[0035] Preferably, the ring A is substituted with methylenedioxy at the 6- and 7-positions of the quinoline ring; the same or different alkoxy groups, in particular methoxy; or the same or different two alkoxy groups, in particular two methoxy groups at the 6- and 7-positions of the quinoline ring.

[0036] Preferably, the ring B is substituted with methylenedioxy; at least one alkoxy group, in particular methoxy; the same or different two alkoxy groups, in particular two methoxy groups; methoxy groups at the 3- or 4-position; or two methoxy groups at the 3- and 4-positions.

[0037] The optionally oxidized sulfur atom represented by X includes a sulfur atom, a sulfinyl group, a sulfonyl group and a group of the formula: $-(CH_2)_q-$ in which q is an integer of 0 to 5, q is preferably 0 or 1;

k is preferably 0.

[0038] Preferred examples of the compound of the formula (I) or a salt thereof include:

3-acetyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline,
3-acetyl-2-(N-tert-butyl-N-ethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline,

or salts thereof.

[0039] The salt of the compound of the formula (I) used in the present invention is preferably a pharmaceutically acceptable salt. Examples thereof include salts with inorganic bases, organic bases, inorganic acids, organic acids, basic or acidic amino acids.

[0040] Preferred examples of the salts with inorganic bases include alkaline metal salts such as a sodium salt, a potassium salt; alkaline earth metal salts such as a calcium salt, a magnesium salt, an aluminium salt, and an ammonium salt.

[0041] Preferred examples of the salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine.

[0042] Preferred examples of the salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid.

[0043] Preferred examples of the salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid.

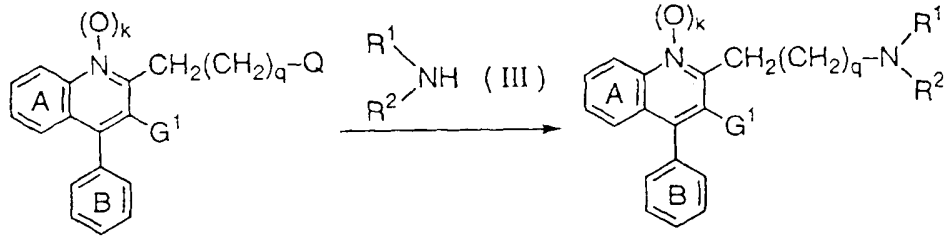
[0044] Preferred examples of the salts with basic amino acids include salts with arginine, lysine and ornithine.

[0045] Preferred examples of the salts with acidic amino acids include aspartic acid and glutamic acid.

[0046] The compound (I) (i.e., the compound of the formula (I); the compounds of other formulas are hereinafter sometimes abbreviated likewise) can be prepared, for example, as follows.

[0047] The desired salt of the compound (I) can be prepared by per se known method from the corresponding free compound or other salt.

Method A



(II-1) (I-1)

wherein Q is a leaving group, G is an acyl group, and the other symbols are as defined above.

[0048] The leaving group represented by Q in the formula (II-1) includes, for example, halogen (preferably chlorine, bromine, iodine), a hydroxyl group activated by esterification such as an organic sulfonic acid residue (e.g., p-toluenesulfonyloxy, methanesulfonyloxy) and an organic phosphoric acid residue (e.g., diphenylphosphoryloxy, dibenzylphosphoryloxy, dimethylphosphoryloxy).

[0049] In this method, the compound (II-1) is reacted with the compound (III) in the presence of a base to prepare the compound (I-1). This reaction is carried out in an appropriate solvent. Examples of the solvent include aromatic hydrocarbons (e.g., benzene, toluene, xylene,), ethers (e.g., dioxane, tetrahydrofuran, dimethoxyethane), alcohols (e.g., methanol, ethanol, propanol), ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone and 2-butanone, and mixed solvents thereof.

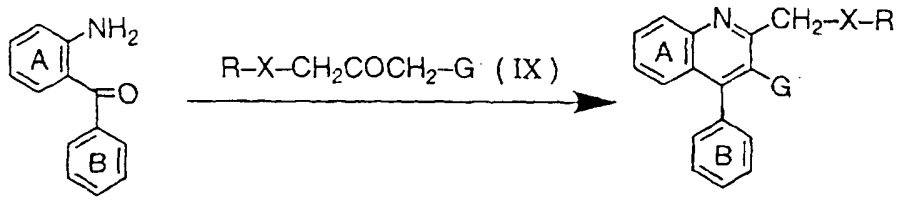
[0050] This reaction is carried out in the presence of an appropriate base such as an alkaline metal salt (e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate), amine (e.g., pyridine, triethylamine, N,N-dimethylaniline), sodium hydride and potassium hydride. The amount of the base to be used is preferably 1 to 5 mol per mol of the compound (II-1). This reaction may be carried out using an excess amount of the

compound (III) as a base.

[0051] The reaction temperature is normally -20° to 150°C, preferably about -10° to 100°C. The reaction time is normally 0.5 hour to 100 hours, preferably 1 hour to 50 hours.

[0052] The compound (I-1) thus obtained can be isolated and purified by conventional separation and purification techniques such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, redistribution and chromatography.

Method E



(VIII) (I–6)

wherein each symbol is as defined above.

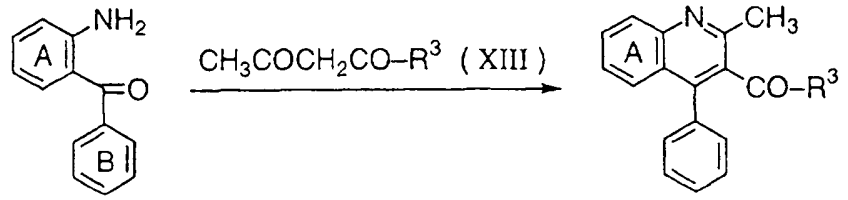
[0053] In this method, 2-aminobenzophenone derivative (VIII) is reacted with the compound (IX) in the presence of an acid to give the compound (I-6). This reaction is carried out in an appropriate solvent. Examples of the solvent include aromatic hydrocarbons (e.g., benzene, toluene and xylene), ethers (e.g., dioxane, tetrahydrofuran and dimethoxyethane), alcohols (e.g., methanol, ethanol and propanol, 2-methoxyethanol), N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and acetic acid.

[0054] This reaction is carried out in the presence of an appropriate acid such as Lewis acid (e.g., aluminium chloride, and zinc chloride,), hydrochloric acid, sulfuric acid, trifluoroacetic acid and p-toluenesulfonic acid. The amount of the acid to be used is preferably 0.05 to 2.0 mol per mol of the compound (VIII). The reaction temperature is normally 20° to 200° C, preferably about 30° to 150° C. The reaction time is 0.5 to 20 hours, preferably 1 to 10 hours.

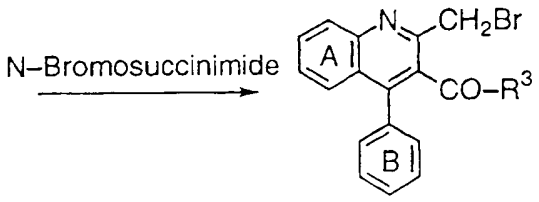
[0055] The compound (I-6) thus obtained can be isolated and purified by conventional separation and purification techniques such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, redistribution and chromatography.

[0056] The compound (II) can be prepared, for example, as follows.

Method J



(VIII) (XIV)



(II–3)

wherein each symbol is as defined above.

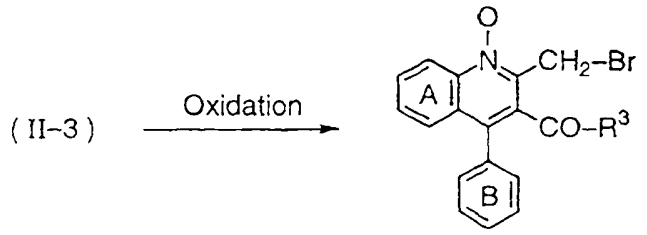
[0057] In this method, the 2-aminobenzophenone derivative (VIII) is reacted with the compound (XIII) in the presence of an acid to give the compound (XIV). The compound (XIV) is then brominated to give the compound (II-3). The reaction of the compound (VIII) with the compound (XIII) can be carried out according to the same manner as that of Method E.

[0058] Then, the compound (XIV) is brominated to give the 2-bromomethylquinoline derivative (II-3). The bromination of the compound (XIV) is carried out according to a conventional method, for example, by reacting it with N-bromosuccinimide, etc., in an appropriate solvent. Examples of the solvent include halogenated hydrocarbons such as carbon tetrachloride, chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2,-tetrachloroethane. The amount of N-bromosuccinimide to be used is 1 to 2 mol per mol of the compound (XIV).

[0059] The bromination is carried out in the presence of a free-radical- initiator such as benzoyl peroxide and 2,2'-azobis(isobutyronitrile). The amount of the free-radical initiator to be used is preferably about 0.001 to 0.01 mol per mol of the compound (XIV). The reaction temperature is normally 20° to 150°C, preferably 30° to 100°C. The reaction time is 0.5 to 20 hours, preferably 1 to 10 hours.

[0060] The compound (II-3) thus obtained can be isolated and purified by conventional separation and purification techniques such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, redistribution and chromatography.

Method L



(II-5)

wherein each symbol is as defined above.

[0061] In this method, the compound (II-3) is oxidized to give the 1-oxide (II-5). This oxidation is carried out according to a conventional method using an oxidizing agent such as m-chloroperbenzoic acid, hydrogen peroxide, peresters, and sodium metaperiodate. This oxidation is preferably carried out in an organic solvent that is inert in the reaction conditions, such as halogenated hydrocarbons (e.g., methylene chloride, chloroform and dichloroethane), hydrocarbons (e.g., benzene and toluene), and alcohols (e.g., methanol, ethanol and propanol). The amount of the oxidizing agent to be used is 1 to 5 mol, preferably 1 to 3 mol, per mol of the compound (II-3). The reaction temperature is -10° to 150°C, preferably 0° to 100°C. The reaction time is normally 0.5 to 10 hours.

[0062] The quinoline 1-oxide derivative (II-5) thus obtained can be isolated and purified by conventional separation and purification techniques such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, redistribution and chromatography.

[0063] The compound (I) or a salt thereof in the present invention has anti-inflammatory activity, and antipyretic and analgesic activity. In addition, it has been confirmed that the compound (I) or a salt thereof has potent antiarthritic activity in an experimental model with adjuvant arthritis in which similar symptoms to those of human rheumatoid arthritis develop. Further, the compound (I) or a salt thereof in the present invention has low toxicity and a low risk of side effect. Thus, the compound (I) or a salt thereof of the present invention is safely applicable to the prevention and treatment of all arthritis exhibiting inflammatory symptoms in joints of mammals such as humans, mice, rats, cats, dogs, rabbits, bovines, swine, sheep and monkeys.

[0064] The compound (I) or a salt thereof of the present invention can be formulated with a pharmaceutically acceptable carrier and administered orally or parenterally as solid preparations such as tablets, capsules, granules, powders, etc; or liquid preparations such as syrups and injections.

[0065] As the pharmaceutically acceptable carrier, various organic or inorganic carrier materials conventionally used for pharmaceutical preparations can be used, and formulated as excipients, lubricants, binders, disintegrators, etc., for solid preparations; solvents, solution adjuvants, suspending agents, tonicity agents, buffering agents, soothing agents, etc., for liquid preparations. If necessary, pharmaceutical additives such as antiseptics, antioxidants, colorants, and sweetening agents can be used.

[0066] Preferred examples of the excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose and light anhydrous silicic acid.

[0067] Preferred examples of the lubricant include magnesium stearate, calcium stearate, talc and colloidal silica.

[0068] Preferred examples of the binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone.

[0069] Preferred examples of the disintegrator include starch, carboxymethylcellulose, carboxymethyl cellulose calcium, croscarmellose sodium and carboxymethyl starch sodium.

[0070] Preferred examples of the solvent include water for injection, alcohols, propylene glycol, macrogol, sesame oil, and corn oil.

[0071] Preferred examples of the solution adjuvant include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

[0072] Preferred examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

[0073] Preferred examples of the tonicity agent include sodium chloride, glycerin and D-mannitol.

[0074] Preferred examples of the buffering agent include buffers such as phosphates, acetates, carbonates and citrates.

[0075] Preferred examples of the soothing agent include benzyl alcohol.

[0076] Preferred examples of the antiseptics include parahydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

[0077] Preferred examples of the antioxidant include sulfites and ascorbic acid.

[0078] The dose of the compound (I) or a salt thereof of the present invention can appropriately be selected depending upon the administration route, condition of the patient to be treated and other factors. Normally, the dose can be selected from the regions of 5 mg to 1000 mg, preferably 10 mg to 500 mg, per an average adult (b.w. 60 kg) per day in the case of oral administration, and 1 mg to 100 mg, preferably 5 to 50 mg, per an average adult (b.w. 60 kg) per day in the case of parenteral administration. The compound in the above dose can be administered daily in one to three divided portions.

[0079] As described above, the present invention provides a novel quinoline derivative having potent anti-inflammatory activity, and antipyretic and analgesic activity as well as low toxicity. In addition, the present invention provides an anti-inflammatory pharmaceutical composition that is applicable to all arthritis exhibiting inflammatory symptoms in joints.

[0080] The following experiments, reference examples, and examples further illustrate the present invention in detail, but are not to be construed to limit the scope thereof.

[0081] The following experiment illustrates the pharmacological activity of the compound (I) or its salt of the present invention.

Experiment 1

Effects on rat adjuvant arthritis

[0082] Male Lewis rats (7 weeks old, Charles River Japan Inc.) were sensitized by injecting Freund's complete adjuvant (a 0.5% suspension of killed Mycobacterium tuberculosis in liquid paraffin)(0.05 ml) intradermally into a plantar part of a right hind leg. A test drug (3.125 mg/kg) was suspended in 0.5% methylcellulose, and orally administered once a day for 14 days. The administration was started just before the sensitization (Day 0). The left hind leg volume and the body weight were measured just before the sensitization (Day 0) and on the 14th day, and the plantar edema inhibitory rate (%) and the body weight gain rate (%) based on those of non-sensitized rat groups were calculated.

[0083] The results are indicated in each group's mean (N=6) ± S.E., and assessed by Dunnett's test. The risk rate of less than 5% was evaluated as significant. As shown in Table 1, the compound of the present invention was effective in improving systemic symptoms observed as plantar edema inhibition and body weight gains.

Table 1

Compound	Edema inhibitory rate (%)	Body weight gain rate [1] (%)
1	52 **	17 **

1) $\frac{\text{(Drug administered rats) - (Sensitized control rats)}}{\text{(Normal control rats) - (Sensitized control rats)}} \times 100$

**, $p<0.01$ vs control

Reference Example 1

[0084] Conc. sulfuric acid (0.185 ml) was added to a mixture of 2-amino-4,5,3',4'-tetramethoxybenzophenone (10.0 g), acetylacetone (3.78 g) and acetic acid (75 ml), and the mixture was stirred at 100°C for 2.5 hours. The reaction mixture was concentrated under reduced pressure. The residue was poured into water and made alkaline with 2N sodium hydroxide, and extracted with chloroform. The chloroform layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform-ethanol (20:1, v/v) gave 3-acetyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methylquinoline (9.78 g, 82%). This compound was recrystallized from dichloromethane-ethanol to give colorless prisms, mp. 210-211°C.

Reference Example 2

[0085] A mixture of 3-acetyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methylquinoline (8.5 g), N-bromosuccinimide (5 mg), 2,2'-azobis(isobutyronitrile)(1.46 g) and carbon tetrachloride (500 ml) was stirred under reflux for 40 minutes. The reaction mixture was cooled, and then the insoluble material was filtered off. The filtrate was washed with water

and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform-ethyl acetate (20:1, v/v) gave 3-acetyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (6.85 g, 67%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 181-182°C.

Reference Example 3

[0086] A mixture of 2-amino-4,5,3',4'-tetramethoxybenzophenone hydrochloride (2.0 g), benzoylacetone (0.917 g) and ethanol (35 ml) was stirred under reflux for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was poured into a saturated aqueous solution of sodium bicarbonate, and the mixture was extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform-ethyl acetate (10:1, v/v) gave 3-benzoyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methylquinoline (1.75 g, 70%). This compound was recrystallized from ethanol to give colorless prisms, mp. 151-152°C.

Reference Example 4

[0087] A mixture of 2-amino-4,5,3',4'-tetramethoxybenzophenone (25.0 g), 1,3-dichloroacetone (11.0 g), conc. sulfuric acid (1.2 ml) and acetic acid (200 ml) was stirred at 110°C for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was poured into water, made alkaline with 2N NaOH, and extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform-ethyl acetate (10:1, v/v) gave 3-chloro-2-chloromethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (12.0 g, 38%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 206-207°C.

Reference Example 5

[0088] A mixture of 3-benzoyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methylquinoline (5.5 g), N-bromosuccinimide (2, 42 g), 2,2'-azobis(isobutyronitrile)(0.815 g) and carbon tetrachloride (250 ml) was stirred under reflux for 1.5 hours. The reaction mixture was cooled, and then the insoluble material was filtered off. The filtrate was washed with water and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform-ethyl acetate (10:1, v/v) gave 3-benzoyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (2.73 g, 42%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 182-183°C.

Reference Example 6

[0089] A mixture of 2-amino-3',4',4,5-tetramethoxybenzophenone hydrochloride (25.0 g), 2,4-octanedione (10.5 g) and ethanol (500 ml) was stirred under reflux for 2 hours. The solvent was evaporated under reduced pressure. The residue was poured into saturated aqueous sodium bicarbonate solution, and extracted with chloroform. The chloroform layer was washed with water and dried over magnesium sulfate. The chloroform was evaporated, and the residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform-ethanol (20:1, v/v) gave 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-3-valerylquinoline. This compound was recrystallized from ethanol to give colorless prisms. mp. 119-120°C.

Reference Example 7

[0090] According to the same manner as that described in Reference Example 6, 2-amino-3',4',4,5-tetramethoxybenzophenone hydrochloride was reacted with 2,4-nonanedione to give 4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxy-2-methylquinoline. This compound was recrystallized from ethanol to give colorless prisms. mp. 123-125°C.

Reference Example 8

[0091] According to the same manner as that described in Reference Example 6, 2-amino-3',4',4,5-tetramethoxybenzophenone hydrochloride was reacted with 6-methyl-2,4-heptanedione to give 4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxy-2-methylquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 135-137°C.

Reference Example 9

[0092] According to the same manner as that described in Reference Example 5, 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-3-valerylquinoline was brominated with N-bromosuccinimide (NBS) to give 2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-valerylquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 150-151°C.

Reference Example 10

[0093] According to the same manner as that described in Reference Example 5, 4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxy-2-methylquinoline was brominated with N-bromosuccinimide (NBS) to give 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxyquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 146-147°C.

Reference Example 11

[0094] According to the same manner as that described in Reference Example 5, 4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxy-2-methylquinoline was brominated with N-bromosuccinimide (NBS) to give 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxyquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 159-161°C.

Example 1

[0095] A mixture of 3-acetyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (3.0 g), diethylamine (4.76 g) and dichloromethane (50 ml) was stirred under reflux for 14 hours. The reaction mixture was washed with water, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform gave 3-acetyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (2.07 g, 73%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 146-148°C.

Reference Example 12

[0096] 3-Acetyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (0.5 g) was added to an ice-cooled suspension of lithium aluminum hydride (0.045 g) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 20 minutes. Then, water (0.3 ml) was added, and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform-ethanol (20:1, v/v) gave 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-3-(1-hydroxyethyl)-6,7-dimethoxyquinoline (0.23 g, 45%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 144-145°C.

Reference Example 13

[0097] Oily sodium hydride (60%, 0.372 g) was added to a solution of 1H-1,2,4-triazole (0.594 g) in N,N-dimethylformamide (30 ml), and the mixture was stirred at room temperature for 15 minutes. Then, 3-acetyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (3.3 g) was added, and the mixture was stirred at 80°C for 40 minutes. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform gave 3-acetyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline (1.4 g, 42%). This compound was recrystallized from ethanol to give colorless prisms, mp. 180-181°C.

Reference Example 14

[0098] A mixture of 3-acetyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (1.5 g), 1-methyl-2-mercaptoimidazole (0.417 g), potassium carbonate (0.495 g) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 3 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried over magnesium sulfate. Evaporation of the solvent gave 3-acetyl-4-(3,4-dimethoxy-phenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline (1.1 g, 71%). This compound

was recrystallized from ethanol to give colorless prisms, mp. 175-176°C.

Reference Example 15

[0099] A mixture of 3-acetyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (1.5 g), morpholine (1.42 g) and dichloromethane (30 ml) was stirred at room temperature for 15 hours. The reaction mixture was washed with water, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform gave 3-acetyl-4-(3,4-dimethoxyphenyl)-2-morpholinomethyl-6,7-dimethoxyquinoline (1.1 g, 72%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 197-199°C.

Example 2

[0100] A mixture of 3-benzoyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (1.5 g), diethylamine (1.05 g) and dichloromethane (40 ml) was stirred under reflux for 14 hours. The reaction mixture was washed with water, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform gave 3-benzoyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (0.97 g, 66%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 150-151°C.

Reference Example 16

[0101] A mixture of 3-chloro-2-chloromethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (2.0 g), diethylamine (2.5 g) and dichloromethane (50 ml) was stirred under reflux for 14 hours. The reaction mixture was washed with water, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silica gel. The fractions eluted with chloroform gave 3-chloro-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline (1.47 g, 67%). This compound was recrystallized from ethyl acetate-hexane to give colorless prisms, mp. 146-148°C.

Reference Example 17

[0102] According to the same manner as that described in Example 4, 3-benzoyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline was reacted with 2-mercapto-1-methylimidazole to give 3-benzoyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline. This compound was recrystallized from ethanol to give colorless prisms, mp. 185-186°C.

Reference Example 18

[0103] According to the same manner as that described in Example 3, 3-benzoyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline was reacted with imidazole to give 3-benzoyl-4-(3,4-dimethoxyphenyl)-2-(1-imidazolylmethyl)-6,7-dimethoxyquinoline. This compound was recrystallized from ethanol to give colorless prisms, mp. 214-215°C.

Example 3

[0104] According to the same manner as that described in Example 1, 3-acetyl-2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline was reacted with N-tert-butyl-N-ethylamine to give 3-acetyl-2-(N-tert-butyl-N-ethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline. This compound was recrystallized from methanol to give colorless prisms, mp. 156-157°C.

Example 4

[0105] According to the same manner as that described in Example 1, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-valerylquinoline was reacted with N-tert-butyl-N-ethylamine to give 4-(3,4-dimethoxyphenyl)-2-(N-tert-butyl-N-ethylaminomethyl)-6,7-dimethoxy-3-valerylquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms, mp. 137-139°C.

Reference Example 19

[0106] According to the same manner as that described in Reference Example 15,2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-valerylquinoline was reacted with morpholine to give 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-morpholinomethyl-3-valerylquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 137-138°C.

Example 5

[0107] According to the same manner as that described in Example 1, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-hexanoylquinoline was reacted with diethylamine to give 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxyquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 104-106°C.

Reference Example 20

[0108] According to the same manner as that described in Ref. Example 15, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxyquinoline was reacted with morpholine to give 4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxy-2-morpholinomethylquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 154-155°C.

Reference-Example 21

[0109] According to the same manner as that described in Ref. Example 15, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxyquinoline was reacted with morpholine to give 4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxy-2-morpholinomethylquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 138-140°C.

Reference Example 22

[0110] According to the same manner as that described in Ref. Example 14, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-isovalerylquinoline was reacted with 2-mercapto-1-methylimidazole to give 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]-3-valerylquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 125-127°C.

Reference Example 23

[0111] According to the same manner as that described in Ref. Example 14,2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxyquinoline was reacted with 2-mercapto-1-methylimidazole to give 4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline. This compound was recrystallized from ethanol to give colorless prisms. mp. 128-129°C.

Reference Example 24

[0112] According to the same manner as that described in Ref. Example 14, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxyquinoline was reacted with 2-mercapto-1-methylimidazole to give 4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxy-2-[(1-methylimidazol-2-yl)thiomethyl]quinoline. This compound was recrystallized from ethanol to give colorless prisms. mp. 152-153°C.

Reference Example 25

[0113] According to the same manner as that described in Ref. Example 13, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-valerylquinoline was reacted with imidazole to give 4-(3,4-dimethoxyphenyl)-2-(1-imidazolylmethyl)-6,7-dimethoxy-3-valerylquinoline. This compound was recrystallized from ethanol to give colorless prisms. mp. 156-157 C.

Reference Example 26

[0114] According to the same manner as that described in Ref. Example 13, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxyquinoline was reacted with imidazole to give 4-(3,4-dimethoxyphenyl)-2-(1-imidazolylmethyl)-3-isovarelyl-6,7-dimethoxyquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 180-181°C.

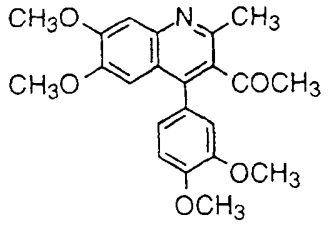
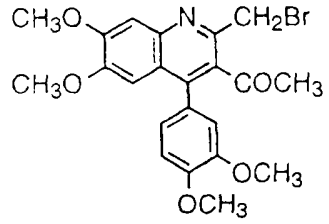
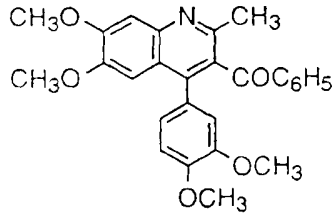
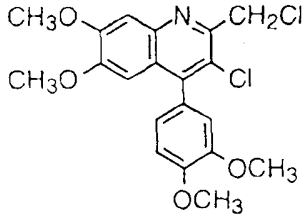
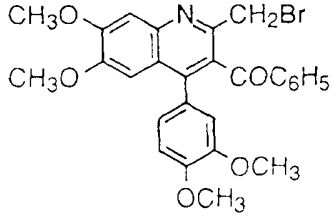
Reference Example 28

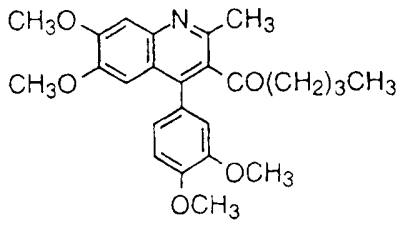
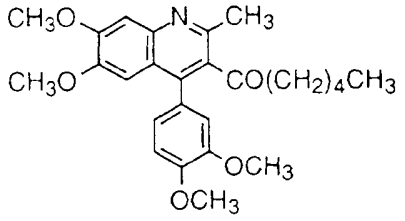
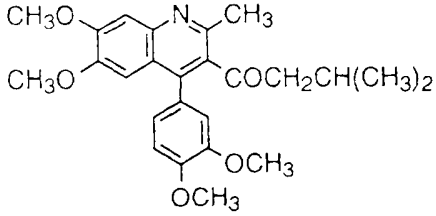
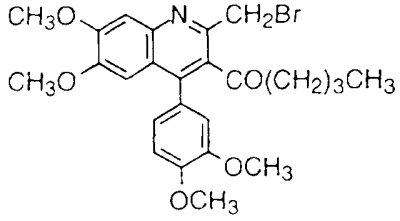
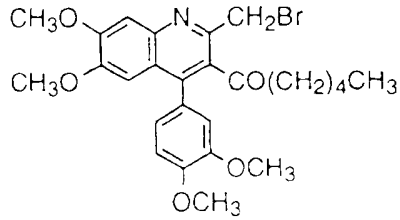
[0115] According to the same manner as that described in Ref. Example 13, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxyquinoline was reacted with 1H-1,2,4-triazole to give 4-(3,4-dimethoxyphenyl)-3-hexanoyl-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline. This compound was recrystallized from ethanol to give colorless prisms. mp. 151-152°C.

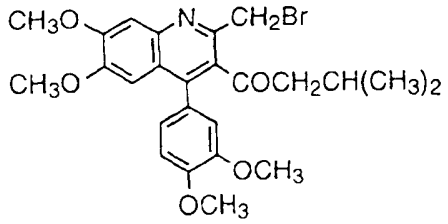
Example 6

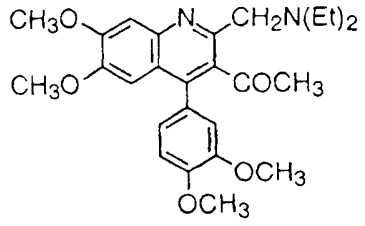
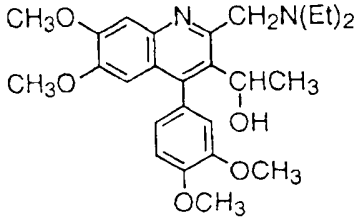
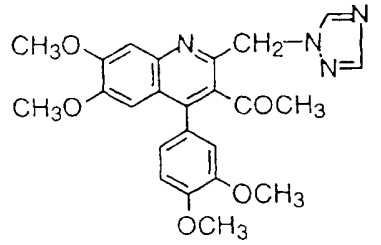
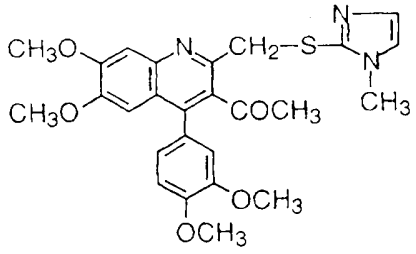
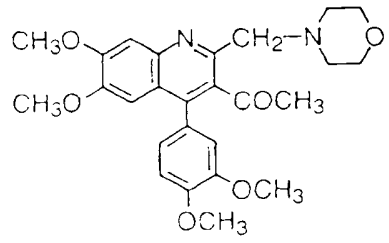
[0116] According to the same manner as that described in Example 1, 2-bromomethyl-4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxyquinoline was reacted with diethylamine to give 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-3-isovaleryl-6,7-dimethoxyquinoline. This compound was recrystallized from ethyl acetate - hexane to give colorless prisms. mp. 153-154°C.

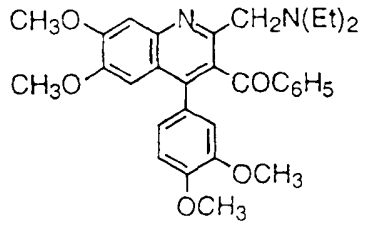
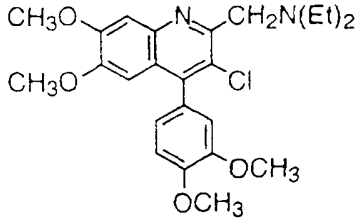
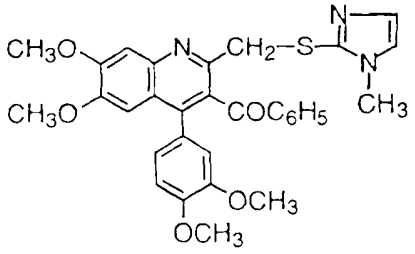
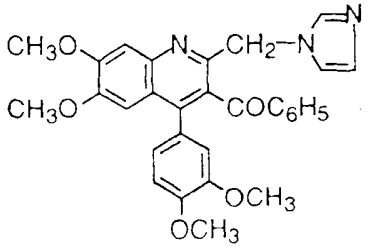
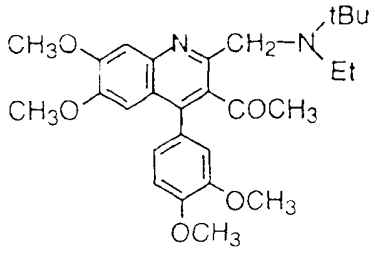
[0117] The chemical formulas of the compounds obtained in Reference Examples (Ref.) and Examples (Ex.) above are listed in the following tables. In the tables, Et means ethyl, and tBu means tert-butyl.

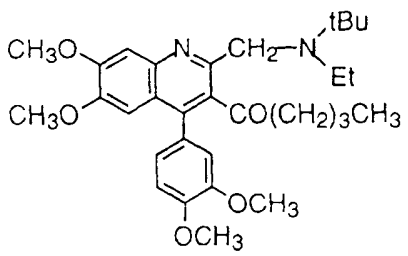
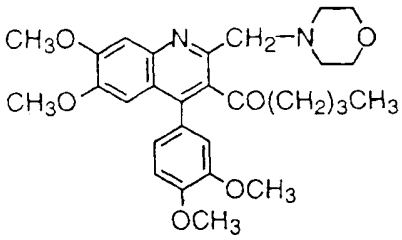
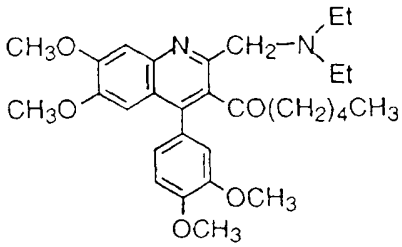
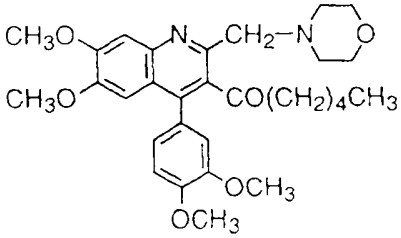
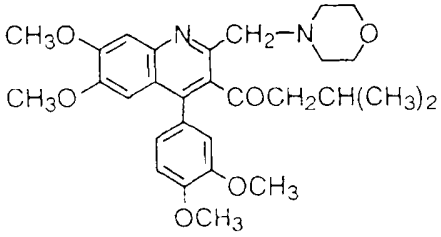
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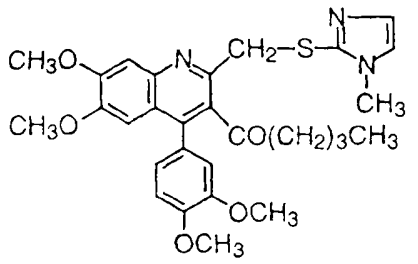
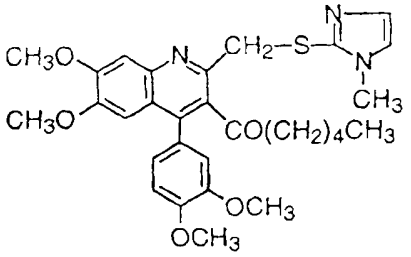
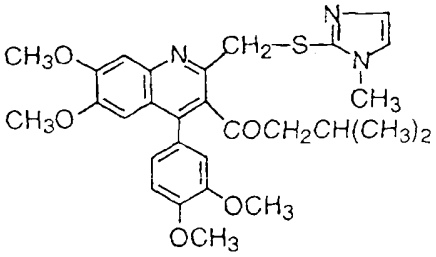
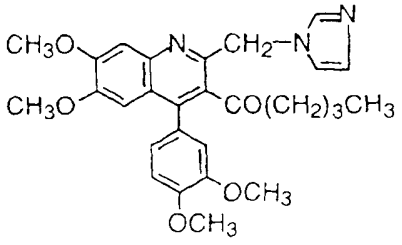
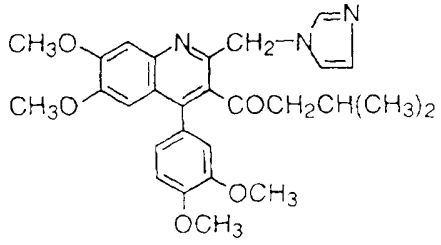
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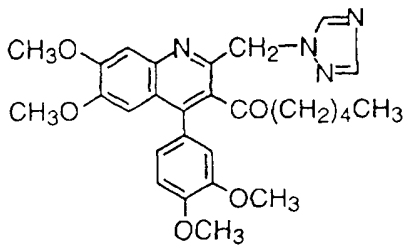
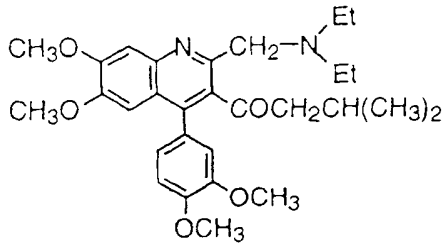
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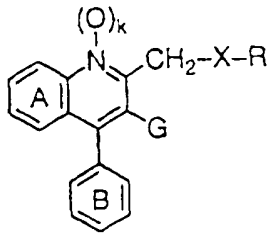
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Claims

1. A compound of the formula (I):



(I)

wherein

G is an acyl group of the formula: -CO-R^3 in which R^3 is a C_{1-5} alkyl group;

X is an oxygen atom, a thio group, a sulfinyl group, a sulfonyl group or a group of the formula: -$(CH_2)_q$- in which q is an integer of 0 to 5;

R is an optionally substituted amino group of the formula: -N(R^1) (R^2) in which R^1 and R^2 are, the same or different,

(1) a hydrogen atom or
(2) an optionally substituted hydrocarbon group, the hydrocarbon group in the optionally substituted hydrocarbon group being a group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{3-7} cycloalkyl,

wherein the substituent(s) to the hydrocarbon group are one to three substituents of

(1) a halogen atom,
(2) a C_{1-10} alkyl group,

(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group,

each of rings A and B may have one to four substituents selected from

(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group,

and further, rings A and B may have a substituent of $-O-(CH_2)_L-O-$, wherein L is an integer of 1 to 3, which forms a ring with mutually adjacent two carbons of the ring A or B;

k is 0 or 1, or a salt thereof.

2. The compound according to claim 1, wherein G' is an acetyl group, or a salt thereof.

3. The compound according to claim 1, wherein the ring A is substituted with at least one alkoxy group, or a salt thereof.

4. The compound according to claim 3, wherein the ring A is substituted with the same or different two alkoxy groups, or a salt thereof.

5. The compound according to claim 4, wherein the ring A is substituted with two alkoxy groups at the 6- and 7-positions of the quinoline ring, or a salt thereof.

6. The compound according to claim 1, wherein the ring B is substituted with at least one alkoxy group, or a salt thereof.

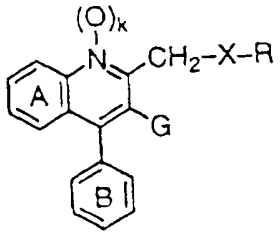
7. The compound according to claim 6, wherein the ring B is substituted with the same or different two alkoxy groups, or a salt thereof.

8. The compound according to claim 7, wherein the ring B is substituted with two alkoxy groups at the 3- and 4-positions, or a salt thereof.

9. The compound according to claim 1, wherein k is 0, or a salt thereof.

10. The compound according to claim 1, which is 3-acetyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline, or a salt thereof.

11. A pharmaceutical composition comprising a compound of the formula (I):



(I)

wherein

G is an acyl group of the formula: $-CO-R^3$ in which R^3 is a C_{1-5} alkyl group;

X is an oxygen atom, a thio group, a sulfinyl group or a sulfonyl group or a group of the formula: $-(CH_2)_q-$ in which q is an integer of 0 to 5;

R is an optionally substituted amino group of the formula: $-N(R^1)(R^2)$ in which R^1 and R^2 are, the same or different,

(1) a hydrogen atom or
(2) an optionally substituted hydrocarbon group, the hydrocarbon group in the optionally substituted hydrocarbon group being a group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{3-7} cycloalkyl,

wherein the substituent(s) to the hydrocarbon group are one to three substituents of

(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group, and
(4) a thiol group or a C_{1-10} alkylthio group;

each of rings A and B may have one to four substituents selected from

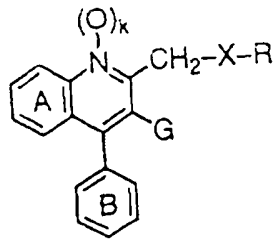
(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group, and
(4) a thiol group or a C_{1-10} alkylthio group,

and further rings A and B may have a substituent of $-O-(CH_2)_L-O-$,
wherein L is an integer of 1 to 3, which forms a ring with mutually adjacent two carbons of the ring A or B;

k is 0 or 1,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. An anti-inflammatory composition for pharmaceutical use, which comprises a compound of the formula (I):



(I)

wherein

G is an acyl group of the formula: $-CO-R^3$ in which R^3 is a C_{1-5} alkyl group;

X is an oxygen atom, a thio group, a sulfinyl group, a sulfonyl group or a group of the formula: $-(CH_2)_q-$ in which q is an integer of 0 to 5;

R is an optionally substituted amino group of the formula:
$-N(R^1)(R^2)$ in which R^1 and R^2 are the same or different,

(1) a hydrogen atom or
(2) an optionally substituted hydrocarbon group, the hydrocarbon group in the optionally substituted hydrocarbon group being a group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{3-7} cycloalkyl,

wherein the substituent(s) to the hydrocarbon group are one to three substituents of

(1) a halogen atom,

(2) a C_{1-10} alykl group,
(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group;

each of rings A and B may have one to four substituents selected from

(1) a halogen atom,
(2) a C_{1-10} alkyl group,
(3) a hydroxy group or a C_{1-10} alkoxy group and
(4) a thiol group or a C_{1-10} alkylthio group,

and further rings A and B may have a substituent of $-O-(CH_2)_L-O-$, wherein L is an integer of 1 to 3, which forms a ring with mutually adjacent two carbons of the ring A or B;

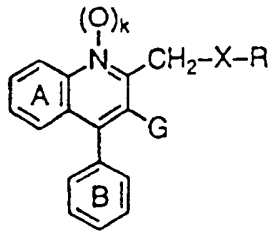
k is 0 or 1,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. Use of a compound of the formula (I) or a salt thereof in the manufacture of anti-inflammatory compositions for pharmaceutical use.

Patentansprüche

1. Verbindung der Formel (I):



(I)

wobei

G eine Acylgruppe der Formel $-CO-R^3$ ist, wobei R^3 eine C_{1-5}-Alkylgruppe ist;

X ein Sauerstoffatom, eine Thiogruppe, eine Sulfinylgruppe, eine Sulfonylgruppe oder eine Gruppe der Formel $-(CH_2)_q-$, wobei q eine ganze Zahl von 0 bis 5 ist, ist;

R eine gegebenenfalls substituierte Aminogruppe der Formel $-N(R^1)(R^2)$ ist, wobei R^1 und R^2 gleich oder verschieden sind, und zwar:

(1) ein Wasserstoffatom oder
(2) eine gegebenenfalls substituierte Kohlenwasserstoffgruppe, wobei die Kohlenwasserstoffgruppe in der gegebenenfalls substituierten Kohlenwasserstoffgruppe eine Gruppe ist, die aus C_{1-8}-Alkyl, C_{2-8}-Alkenyl und C_{3-7}-Cycloalkyl ausgewählt ist;

wobei die Substituenten an der Kohlenwasserstoffgruppe ein bis drei der folgenden Substituenten sind:

(1) ein Halogenatom;
(2) eine C_{1-10}-Alkylgruppe;
(3) eine Hydroxygruppe oder eine C_{1-10}-Alkoxygruppe, und

(4) eine Thiolgruppe oder eine C_{1-10}-Alkylthiogruppe;

wobei jeder der Ringe A und B einen bis vier Substituenten haben kann, die ausgewählt sind aus:

(1) einem Halogenatom;
(2) einer C_{1-10}-Alkylgruppe;
(3) einer Hydroxygruppe oder einer C_{1-10}-Alkoxygruppe; und
(4) einer Thiolgruppe oder einer C_{1-10}-Alkylthiogruppe;

und die Ringe A und B weiterhin einen Substituenten $-O-(CH_2)_L-O-$ haben können, wobei L eine ganze Zahl von 1 bis 3 ist, die mit zwei einander benachbarten Kohlenstoffatomen des Rings A oder B einen Ring bildet;

k 0 oder 1 ist;

oder ein Salz davon.

2. Verbindung gemäß Anspruch 1, wobei G' eine Acetylgruppe ist, oder ein Salz davon.

3. Verbindung gemäß Anspruch 1, wobei Ring A mit wenigstens einer Alkoxygruppe substituiert ist, oder ein Salz davon.

4. Verbindung gemäß Anspruch 3, wobei Ring A mit zwei gleichen oder verschiedenen Alkoxygruppen substituiert ist, oder ein Salz davon.

5. Verbindung gemäß Anspruch 4, wobei Ring A mit zwei Alkoxygruppen in der 6- und 7-Position des Chinolinrings substituiert ist, oder ein Salz davon.

6. Verbindung gemäß Anspruch 1, wobei Ring B mit wenigstens einer Alkoxygruppe substituiert ist, oder ein Salz davon.

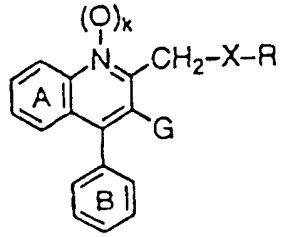
7. Verbindung gemäß Anspruch 6, wobei Ring B mit zwei gleichen oder verschiedenen Alkoxygruppen substituiert ist, oder ein Salz davon.

8. Verbindung gemäß Anspruch 7, wobei Ring B mit zwei Alkoxygruppen in der 3- und 4-Position substituiert ist, oder ein Salz davon.

9. Verbindung gemäß Anspruch 1, wobei k 0 ist, oder ein Salz davon.

10. Verbindung gemäß Anspruch 1, bei der es sich um 3-Acetyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxychinolin oder ein Salz davon handelt.

11. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I)



(I)

wobei

G eine Acylgruppe der Formel $-CO-R^3$ ist, wobei R^3 eine C_{1-5}-Alkylgruppe ist;

X ein Sauerstoffatom, eine Thiogruppe, eine Sulfinylgruppe, eine Sulfonylgruppe oder eine Gruppe der Formel $-(CH_2)_q-$, wobei q eine ganze Zahl von 0 bis 5 ist, ist;

R eine gegebenenfalls substituierte Aminogruppe der Formel $-N(R^1)(R^2)$ ist, wobei R^1 und R^2 gleich oder verschieden sind, und zwar:

(1) ein Wasserstoffatom oder
(2) eine gegebenenfalls substituierte Kohlenwasserstoffgruppe, wobei die Kohlenwasserstoffgruppe in der gegebenenfalls substituierten Kohlenwasserstoffgruppe eine Gruppe ist, die aus C_{1-8}-Alkyl, C_{2-8}-Alkenyl und C_{3-7}-Cycloalkyl ausgewählt ist;

wobei die Substituenten an der Kohlenwasserstoffgruppe ein bis drei der folgenden Substituenten sind:

(1) ein Halogenatom;
(2) eine C_{1-10}-Alkylgruppe;
(3) eine Hydroxygruppe oder eine C_{1-10}-Alkoxygruppe; und
(4) eine Thiolgruppe oder eine C_{1-10}-Alkylthiogruppe;

wobei jeder der Ringe A und B einen bis vier Substituenten haben kann, die ausgewählt sind aus:

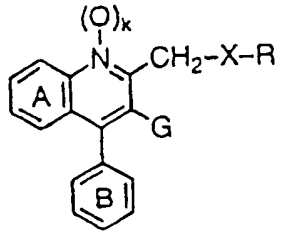
(1) einem Halogenatom;
(2) einer C_{1-10}-Alkylgruppe;
(3) einer Hydroxygruppe oder einer C_{1-10}-Alkoxygruppe; und
(4) einer Thiolgruppe oder einer C_{1-10}-Alkylthiogruppe;

und die Ringe A und B weiterhin einen Substituenten $-O-(CH_2)_L-O-$ haben können, wobei L eine ganze Zahl von 1 bis 3 ist, die mit zwei einander benachbarten Kohlenstoffatomen des Rings A oder B einen Ring bildet;

k 0 oder 1 ist;

oder ein pharmazeutisch annehmbares Salz davon sowie einen pharmazeutisch annehmbaren Träger umfasst.

12. Entzündungshemmende Zusammensetzung zur pharmazeutischen Verwendung, die eine Verbindung der Formel (I)



(I)

wobei

G eine Acylgruppe der Formel $-CO-R^3$ ist, wobei R^3 eine C_{1-5}-Alkylgruppe ist;

X ein Sauerstoffatom, eine Thiogruppe, eine Sulfinylgruppe, eine Sulfonylgruppe oder eine Gruppe der Formel $-(CH_2)_q-$, wobei q eine ganze Zahl von 0 bis 5 ist, ist;

R eine gegebenenfalls substituierte Aminogruppe der Formel $-N(R^1)(R^2)$ ist, wobei R^1 und R^2 gleich oder verschieden sind, und zwar:

(1) ein Wasserstoffatom oder
(2) eine gegebenenfalls substituierte Kohlenwasserstoffgruppe, wobei die Kohlenwasserstoffgruppe in der

gegebenenfalls substituierten Kohlenwasserstoffgruppe eine Gruppe ist, die aus C_{1-8}-Alkyl, C_{2-8}-Alkenyl und C_{3-7}-Cycloalkyl ausgewählt ist;

wobei die Substituenten an der Kohlenwasserstoffgruppe ein bis drei der folgenden Substituenten sind:

(1) ein Halogenatom;
(2) eine C_{1-10}-Alkylgruppe;
(3) eine Hydroxygruppe oder eine C_{1-10}-Alkoxygruppe; und
(4) eine Thiolgruppe oder eine C_{1-10}-Alkylthiogruppe;

wobei jeder der Ringe A und B einen bis vier Substituenten haben kann, die ausgewählt sind aus:

(1) einem Halogenatom;
(2) einer C_{1-10}-Alkylgruppe;
(3) einer Hydroxygruppe oder einer C_{1-10}-Alkoxygruppe; und
(4) einer Thiolgruppe oder einer C_{1-10}-Alkylthiogruppe;

und die Ringe A und B weiterhin einen Substituenten $-O-(CH_2)_L-O-$ haben können, wobei L eine ganze Zahl von 1 bis 3 ist, die mit zwei einander benachbarten Kohlenstoffatomen des Rings A oder B einen Ring bildet;

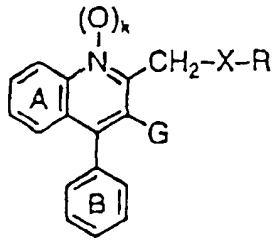
k 0 oder 1 ist;

oder ein pharmazeutisch annehmbares Salz davon sowie einen pharmazeutisch annehmbaren Träger umfasst.

13. Verwendung einer Verbindung der Formel (I) oder eines Salzes davon bei der Herstellung entzündungshemmender Zusammensetzungen für die pharmazeutische Verwendung.

Revendications

1. Composé de formule (I) :



(I)

dans laquelle

G représente un groupe acyle de formule $-CO-R^3$ où R^3 représente un groupe alkyle en C_{1-5} ;
X représente un atome d'oxygène ou de soufre, un groupe sulfinyle ou sulfonyle, ou un groupe de formule $-(CH_2)_q-$ où q représente un nombre entier valant de 0 à 5 ;
R représente un groupe amino éventuellement substitué, de formule $-N(R^1)(R^2)$ où R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun

1) un atome d'hydrogène, ou
2) un groupe hydrocarboné éventuellement substitué, ce groupe hydrocarboné étant choisi parmi les groupes alkyle en C_{1-8}, alcényle en C_{2-8} et cycloalkyle en C_{3-7}, et les substituants que peut porter ce groupe hydrocarbone étant au nombre de 1 à 3 et choisis parmi

1) les atomes d'halogène,
2) les groupes alkyle en C_{1-10},

3) les groupes hydroxy et alcoxy en C_{1-10}, et
4) les groupes thiol et alkylthio en C_{1-10};

les cycles A et B peuvent porter chacun de 1 à 4 substituants choisis parmi

1) les atomes d'halogène,
2) les groupes alkyle en C_{1-10},
3) les groupes hydroxy et alcoxy en C_{1-10}, et
4) les groupes thiol et alkylthio en C_{1-10},

et ces cycles A et B peuvent en outre porter un substituant de formule $-O-(CH_2)_L-O-$ où L représente un nombre entier valant de 1 à 3, lequel substituant constitue un cycle avec deux atomes de carbone mutuellement adjacents du cycle A ou B ;
et k vaut 0 ou 1 ;

ou sel d'un tel composé.

2. Composé conforme à la revendication 1, dans lequel G représente un groupe acétyle, ou sel d'un tel composé.

3. Composé conforme à la revendication 1, dans lequel le cycle A porte au moins un substituant alcoxy, ou sel d'un tel composé.

4. Composé conforme à la revendication 3, dans lequel le cycle A porte deux substituants alcoxy identiques ou différents, ou sel d'un tel composé.

5. Composé conforme à la revendication 4, dans lequel le cycle A porte deux substituants alcoxy en les positions 6 et 7 du cycle quinoléine, ou sel d'un tel composé.

6. Composé conforme à la revendication 1, dans lequel le cycle B porte au moins un substituant alcoxy, ou sel d'un tel composé.

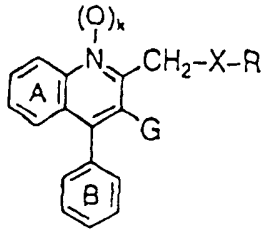
7. Compose conforme à la revendication 6, dans lequel le cycle B porte deux substituants alcoxy identiques ou différents, ou sel d'un tel composé.

8. Compose conforme à la revendication 7, dans lequel le cycle B porte deux substituants alcoxy en positions 3 et 4, ou sel d'un tel composé.

9. Composé conforme à la revendication 1, dans lequel k vaut 0, ou sel d'un tel composé.

10. Composé conforme à la revendication 1, qui est la 3-acétyl-2-(N,N-diéthylaminométhyl)-4-(3,4-diméthoxyphényl)-6,7-diméthoxyquinoléine, ou un sel de ce composé.

11. Composition pharmaceutique contenant un composé de formule (I) :



(I)

dans laquelle

G représente un groupe acyle de formule $-CO-R^3$ où R^3 représente un groupe alkyle en C_{1-5};

X représente un atome d'oxygène ou de soufre, un groupe sulfinyle ou sulfonyle, ou un groupe de formule -$(CH_2)_q$- où q représente un nombre entier valant de 0 à 5 ;
R représente un groupe amino éventuellement substitué, de formule -$N(R^1)(R^2)$ où R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun

1) un atome d'hydrogène, ou
2) un groupe hydrocarboné éventuellement substitué, ce groupe hydrocarboné étant choisi parmi les groupes alkyle en C_{1-8}, alcényle en C_{2-8} et cycloalkyle en C_{3-7}, et les substituants que peut porter ce groupe hydrocarboné étant au nombre de 1 à 3 et choisis parmi

1) les atomes d'halogène,
2) les groupes alkyle en C_{1-10},
3) les groupes hydroxy et alcoxy en C_{1-10}, et
4) les groupes thiol et alkylthio en C_{1-10} ;

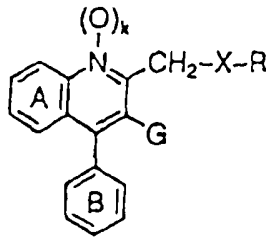
les cycles A et B peuvent porter chacun de 1 à 4 substituants choisis parmi

1) les atomes d'halogène,
2) les groupes alkyle en C_{1-10},
3) les groupes hydroxy et alcoxy en C_{1-10}, et
4) les groupes thiol et alkylthio en C_{1-10}, ces cycles A et B pouvant en outre porter un substituant de formule -O-$(CH_2)_L$-O- où L représente un nombre entier valant de 1 à 3, lequel substituant constitue un cycle avec deux atomes de carbone mutuellement adjacents du cycle A ou B ;

et k vaut 0 ou 1 ;

ou un sel admissible en pharmacie d'un tel composé, et un véhicule admissible en pharmacie.

12. Composition anti-inflammatoire à usage pharmaceutique, qui contient un composé de formule (I) :



(I)

dans laquelle

G représente un groupe acyle de formule -CO-R^3 où R^3 représente un groupe alkyle en C_{1-5} ;
X représente un atome d'oxygène ou de soufre, un groupe sulfinyle ou sulfonyle, ou un groupe de formule -$(CH_2)_q$- où q représente un nombre entier valant de 0 à 5 ;
R représente un groupe amino éventuellement substitué, de formule -$N(R^1)(R^2)$ où R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun

1) un atome d'hydrogène, ou
2) un groupe hydrocarboné éventuellement substitué, ce groupe hydrocarboné étant choisi parmi les groupes alkyle en C_{1-8}, alcényle en C_{2-8} et cycloalkyle en C_{3-7}, et les substituants que peut porter ce groupe hydrocarboné étant au nombre de 1 à 3 et choisis parmi

1) les atomes d'halogène,
2) les groupes alkyle en C_{1-10},
3) les groupes hydroxy et alcoxy en C_{1-10}, et
4) les groupes thiol et alkylthio en C_{1-10} ;

les cycles A et B peuvent porter chacun de 1 à 4 substituants choisis parmi

1) les atomes d'halogène,
2) les groupes alkyle en C_{1-10},
3) les groupes hydroxy et alcoxy en C_{1-10}, et
4) les groupes thiol et alkylthio en C_{1-10},

ces cycles A et B pouvant en outre porter un substituant de formule $-O-(CH_2)_L-O-$ où L représente un nombre entier valant de 1 à 3, lequel substituant constitue un cycle avec deux atomes de carbone mutuellement adjacents du cycle A ou B ;
et k vaut 0 ou 1 ;

ou un sel admissible en pharmacie d'un tel composé, et un véhicule admissible en pharmacie.

13. Utilisation d'un composé de formule (I) ou d'un sel d'un tel composé dans la fabrication de compositions anti-inflammatoires à usage pharmaceutique.